EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Vectormune HVT-AIV (EMEA/V/C/006288/0000)

Vaccine common name: Avian influenza vaccine (live, recombinant)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant, Ceva Sante Animale, submitted on 28 February 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Vectormune HVT-AIV, through the centralised procedure under Article 42(2)a of Regulation (EU) 2019/6 (**mandatory scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 18 January 2023 as Vectormune HVT-AIV has been developed by means of a biotechnological process, i.e. using recombinant DNA technology (Article 42(2)(a)(i)).

At the time of submission, the applicant applied for the following indication:

"For active immunisation of one-day old chickens or 18-19 old embryonated chicken eggs:
- to reduce mortality, clinical signs and virus excretion due to infection with highly pathogenic avian influenza (HPAI) virus of the H5 type
- to reduce mortality, clinical signs and lesions caused by Marek's disease (MD) virus.
- Onset of immunity: HPAI 2 weeks of age
  MD: 5 days
- Duration of immunity: HPAI: 19 weeks
  MD: entire risk period

Considering the legal basis, the claim suggested by the applicant has been modified as follows:

"For active immunisation of one-day old chickens:
- to reduce mortality, clinical signs and virus excretion due to infection with highly pathogenic avian influenza (HPAI) virus of the H5 sub-type
- Onset of immunity: 2 weeks of age
- Duration of immunity: 19 weeks

Vectormune HVT-AIV is a cell-associated, live recombinant vector vaccine for chickens for subcutaneous injection. The vaccine contains one active substance: live turkey herpesvirus, strain rHVT/AI-H5 (FC126, cell-associated), expressing haemagglutinin gene of avian influenza virus subtype H5.

The vaccine is presented as a frozen suspension for injection in flame-sealed ampoules containing 1000, 2000 or 4000 doses. The vaccine is to be reconstituted before use with a sterile diluent to 0.2 ml/dose for subcutaneous use.

The rapporteur appointed is Christine Miras and the co-rapporteur is Leona Nepejchalová.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances.

This legal base was agreed on the basis of the current epidemiological situation of avian influenza in Europe. A claim on Marek's disease was also requested but cannot be supported under this legal base and therefore, no reference to the claim or the data provided to support it are reported in this assessment.

On 12 February 2025, the CVMP adopted an opinion and CVMP assessment report.

On 28 March 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Vectormune HVT-AIV.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Manufacture of the active substance avian influenza and manufacture, primary packaging and quality controls of the frozen live, recombinant suspension take place outside the EEA at the CEVA Animal Health, Lenexa, USA manufacturing site.

The sites responsible for the physical importation are CEVA Phylaxia, Budapest, and CEVA-Phylaxia, Monor in Hungary.

Quality controls for the European market (complete re-testing) and batch release for the frozen suspension are to be performed at CEVA Phylaxia, Budapest, Hungary.

Secondary packaging takes place at CEVA Phylaxia, Budapest, or CEVA-Phylaxia, Monor in Hungary or CEVA Santé Animale, Libourne, France and CEVA Animal Health, Lenexa, USA.

Manufacture, primary packaging and control of the solvent may be performed by Informed Fluids S.R.L., Bucharest, Romania or CEVA-Phylaxia, Budapest, Hungary.

Secondary packaging could take place at both sites or at the CEVA-Phylaxia, Monor Hungary or CEVA Santé Animale, Libourne France site.
CEVA-Phylaxia, Budapest, Hungary is responsible for batch release.

All the above-mentioned sites are GMP compliant and valid certificates have been provided.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

The GMP status of the manufacturing sites located in US and Europe has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Quality documentation (physico-chemical, biological, and microbiological information)

Qualitative and quantitative composition

Vectormune HVT-AIV is a recombinant live vaccine intended for the active immunisation of chickens against avian influenza caused by highly pathogenic avian influenza virus (HPAIV), H5 (hemagglutinin) type.

The live vaccine is presented as a frozen suspension containing, as active substance, a genetically modified live recombinant turkey herpesvirus with an inserted gene (H5) of HPAIV (rHVT/AI-H5) with a minimum titre of 2500 and a maximum titre of 12000 plaque-forming units per dose (PFU/dose).

Other ingredients as medium (EMEM, L-Glutamine), stabilisers (bovine serum), buffers (sodium bicarbonate and HEPES), cryoprotectants (dimethyl sulfoxide-DMSO) and water for injections are included as excipients in the formulation. Trace amounts of gentamicin remain in a single vaccine dose (150 ng/dose) which is considered acceptable. Gentamicin is added along with cryoprotectant 1 to adjust the virus harvest cell suspension to reach the target cell count for blending process of the bulk vaccine. The applicant's manufacturing approach (i.e. use of cryoprotectant 1 + gentamicin) during blending is considered acceptable as the final level of gentamicin per final dose (150 ng) is very low. Confirmation regarding addition of DMSO only as part of cryoprotectant base 2 solution, as well as the absence of gentamicin in cryoprotectant 2 solution, have been provided. No adjuvants are added. The frozen cell concentrate suspension is to be reconstituted with the sterile solvent provided before administration to chickens.

The solvent contains sucrose, casein enzymatic hydrolysate (NZ amine AS), sorbitol, dipotassium hydrogen phosphate and potassium dihydrogen phosphate, phenol red and water for injections.

The vaccine is to be administered via subcutaneous injection after reconstitution of the frozen suspension in sterile solvent.

Container and closure system

The vaccine is filled into sterile 2 ml pre-labelled hydrolytic type I glass ampoules, which are flame sealed, frozen and stored in liquid nitrogen. Different dose presentations are available: 1000, 2000 or 4000 doses.

The liquid solvent is filled in 400, 800, 1000, 1200 or 1600 ml sealed plastic bags made of polyvinylchloride and fitted with an injection and infusion port.

Containers and closures are adequately sterilised.

Product development

The vaccine is a monovalent, cell-associated live vector vaccine that contains one active substance: a genetically-modified live turkey herpesvirus, strain rHVT/AI-H5 which is a serotype 3 Marek's disease virus (FC-126 HVT) modified to express hemagglutinin H5 of avian influenza virus.

The vaccine is currently manufactured, authorised and licensed in the USA. The parent strain of the

vaccine (FC-126 strain of HVT) is a naturally occurring non-pathogenic alpha-herpesvirus originally isolated from domestic turkeys and widely used as vaccine strain to control Marek's disease. Their use is safe as HVT strains are not known to cause disease in any species and do not replicate in mammals.

Inclusion of H5 hemagglutinin allows to immunise against AIV type H5. The cleavage site of the H5 gene was altered to reproduce typical cleavage site sequence of low pathogenic avian influenza strain. This construct has been shown to be protective against different clade H5 viruses including complete different H5 lineage (American). Vaccination-challenge studies have been conducted using a broad spectrum of H5 clades including subclades 2.3.4.4.b. responsible for the current outbreaks in Europe.

The construction of the rHVT/H5 was performed using standard techniques for genetic manipulation and it is fully described.

The manufacturing method, formulation, packaging and storage are described and are similar to other live rHVT and Marek vaccines routinely manufactured by the applicant (propagation in CEF cell culture). All excipients are well known pharmaceutical ingredients. The vaccine does not contain any adjuvant or preservative. An extraneous agents risk assessment is provided.

The use of antibiotics in growth media used during the manufacturing and at final stage of the harvesting and dilution step is acceptable. The finished product contains low level of antibiotics which are far below the levels required to produce pharmacological activity in the target animal, which is considered acceptable.

The formulation of the vaccine is based on the cell count of the virus harvest. The release titre range for the active substance is justified based on clinical data, variability of the testing method and stability data; the justification is discussed in the relevant parts of this document. All pre-clinical and clinical studies were performed with Vectormune HVT-AIV.

The solvent supplied for the reconstitution of the vaccine is the same as already approved for use with other HVT vector vaccines of the same applicant.

Description of the manufacturing method

The manufacturing method can be considered as a standard one for cell-associated vaccines and the same method is already used by the same manufacturer for Marek's disease and recombinant HVT vaccines.

The typical batch size is 50 litres of bulk vaccine.

The active substance is propagated in CEF monolayers prepared from embryonated SPF hen's eggs. CEF cultures are inoculated with thawed working seed virus diluted, incubated and harvested after trypsinisation.

The cell suspension is aseptically collected; cells are spun and supernatant is discarded. Then cells are pooled and resuspended. The resuspended cells are then filtered and collected into a sterile collection container. Based on the cell count, the bulk is supplemented with the required quantity of cryoprotectant to prepare the final vaccine bulk. The use of antibiotics along with one cryoprotectant solution to adjust the pooled cell suspension is considered acceptable as this results in very low levels, far below the levels required to produce pharmacological activity in the target animal.

The bulk vaccine is filled into glass ampoules which are subsequently flame-sealed and then deep frozen. The frozen ampoules are placed into liquid nitrogen or nitrogen vapour for storage.

Batches of finished product are produced with up to 5 passages from the master seed. Data from consecutive vaccine batches are provided.

For the production of the sterile solvent, ingredients are mixed with deionized water until dissolution. pH is adjusted. The solvent is then filled into plastic bags containers and, afterwards, terminally sterilised. Some additional details regarding the manufacturing process would have generally been requested under a standard (Article 8) marketing authorisation. However, the data provided are considered sufficient under an Article 25 authorisation.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Representative certificates of analysis have been provided for all starting materials and, where relevant, most of these conform to specifications of the Ph. Eur. monographs: DMSO, sodium bicarbonate, sodium hydroxide, hydrochloric acid, glucose, potassium dihydrogen phosphate, disodium phosphate, sodium chloride, potassium chloride, sucrose, D-sorbitol, dipotassium hydrogen phosphate potassium di-hydrogen phosphate, phenol red, chicken flocks free from specified pathogens, specific pathogen free (SPF) eggs, bovine serum, amphotericin B, gentamicin sulphate and water for injection.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

Active substance

The master seed virus (MSV) was constructed using genetic manipulation.

The parental organism is the FC-126 strain of HVT obtained from USA (originally isolated from turkeys in 1968).

Donor organism for the HA gene (H5N1) was isolated in Hungary. The cleavage site was altered to reproduce typical cleavage site sequence of low pathogenic avian strain and an HA encoding a polypeptide was inserted. The gene was cloned and engineered.

The recombinant rHVT/AI-H5 was constructed and plaque purified by CEVA. The virus was passed in CEFs during the purification process and passaged additional times before establishment of the Master Seed.

The MSV was characterised and controlled for identity, sterility and extraneous agents (9 CFR (US) methods) and a certain passage of the MSV was tested for extraneous agents according to Ph. Eur. requirements (Ph. 2.6.24 applicable at the time of the testing). Genetic and phenotypic stability of the MSV after passages in CEF cells is confirmed by sequencing.

The working seed virus (WSV) used for the vaccine preparation is produced as described for the finished product. It is controlled for identity and expression of HA protein and sterility.

Other substances of biological origin

Trypsin, tryptose phosphate broth (TPB) powder, bovine serum, and sodium deoxycholate are used during the manufacturing process. The source and origin of these starting materials are described. These materials are treated by gamma irradiation. Certificates of analysis (CoAs) are provided.

Primary CEF cells are used for the production of the vaccine. The cells can be obtained from external suppliers or are prepared in-house from embryonated chicken eggs. Relevant documentation is

provided to support quality of these cells and compliance with Ph. Eur. requirements.

The compliance of the starting materials of animal origin used in the production of the final product with the current regulatory texts related to Ph. Eur. monograph 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" & TSE Note for Guidance (EMEA/410/01 rev.3) has been considered.

A risk assessment regarding the presence of extraneous agents in the finished product has been provided by the applicant and allows to conclude on the absence of risk.

Generally, additional detailed information would have been requested on some raw materials but the information available is acceptable under an Art. 25 authorisation.

Starting materials of non-biological origin

Starting materials of non-biological origin include EMEM powder, L-glutamine, HEPES and phenol red. Example CoAs are provided indicating all materials conform to in-house specifications.

In-house preparation of media and solutions consisting of several components

In-house prepared media used at the different steps of the manufacturing process (culture media, digestion solution, cryoprotective solutions) are described (qualitative and quantitative composition) and, when relevant, appropriate certificates of analysis are provided. Information on storage conditions, controls and sterilisation treatments are provided. All media and solutions are sterile filtered or aseptically prepared and absence of any contaminants in these components is ensured.

Control tests during the manufacturing process

The in-process controls described in the dossier are considered sufficient to control the manufacturing process of the vaccine and the solvent.

During production of the frozen suspension of the vaccine, viability and counting of CEF are controlled before planting. Cells are observed for cytopathic effect after inoculation and cells are counted after harvest. Filling volumes are checked during the filling of ampoules.

During its production, the solvent is controlled for pH and filled volumes are measured during filling.

Control tests on the finished product

The final vaccine is controlled for appearance, sterility, mycoplasma, identity and potency in the CEVA US manufacturing site, and is fully re-controlled according to Ph. Eur. methods and specific potency in CEVA-Phylaxia, Hungary.

The solvent is controlled for appearance, pH, osmolarity, sterility and extractable volume.

Vaccine finished product tests:

Identity and potency are controlled by immunofluorescence staining (Ceva-Lenexa) and black plaque assay on CEF (Ceva-Phylaxia) using monoclonal antibodies specific for HVT and AIV-H5. These are classical methods for this kind of vaccine. Method descriptions have been provided and validation data allow to confirm validity of the methods (specificity, linearity, robustness and equivalence between the titres measured in US or in Europe).

Release limits are justified based on safety and efficacy data and expected variability of the method and stability of the vaccine.

Sterility and absence of mycoplasma are controlled according to Ph. Eur. 2.6.1 ("sterility") and Ph. Eur. 2.6.7. ("Mycoplasma"). A risk-based approach following Ph. Eur. 5.2.5 has been used to demonstrate the absence of extraneous agents and absence of any further testing may be accepted.

Batch-to-batch consistency

Results for six consecutive vaccine batches are provided. Testing was performed as per USDA specifications and it is expected that these batches would pass the EU test re-control on imported batches. Sterility and mycoplasma testing are harmonised, and identity and potency will be tested using the same or equivalent methods.

Results are also provided for three batches of sterile solvent, for each presentation, and these conform to the specifications.

The results presented for vaccine and solvent batches support the consistency of production. Complete batch release protocols (BRPs) for 2 batches tested in Europe are also provided that are fully compliant with specifications.

Stability

Stability of the bulk antigen is not applicable to this vaccine as the finished product is manufactured immediately after antigen production.

Data are provided to support 24-month stability of the vaccine. Seven batches of vaccine containing 1000, 2000 or 4000 doses were investigated for potency at different time points during at most 30 months. The results of the shelf-life study have been taken into account to set the release limits for the active substance. Stability data from one batch controlled in Europe should be provided as specific obligation including results for appearance, pH and sterility at the end of the storage time.

Data are provided that support 30 months stability for the solvent stored at room temperature. Three batches per presentation were investigated and all parameters meet specifications during storage time.

No data are provided on stability of the reconstituted vaccine for this product. Within the frame of a marketing authorisation under exceptional circumstances, it is accepted that data available for another vaccine Vectormune ND (same HVT strain in CEF, similar construct and qualitative and quantitative composition) could support an in-use stability of 2 hours for Vectormune HVT-AIV. The results of the stability of reconstituted Vectormune ND have been taken into account to set release titre for Vectormune HVT-AIV. Further data on the in-use stability of the vaccine should be provided post-marketing authorisation (specific obligation).

Overall conclusions on quality

Vectormune HVT-AIV is a live recombinant vaccine for the active immunisation of chickens against avian influenza. The vaccine is a frozen suspension in glass ampoules containing 1000, 2000 or 4000 doses to be reconstituted before use in sterile diluent supplied in plastic bags. The active ingredient is cell-associated live recombinant virus strain rHVT/AI-H5.

Information on the development, manufacture and control of the active substance and the finished

product have been provided by the applicant. The production method, including in-process controls and controls of the finished product ensure, in principle, a consistent quality of the vaccine batches.

The virus is grown on chicken embryo fibroblast cells produced from embryos obtained from SPF chicken flocks. The manufacturing method can be considered as standard for this type of vaccine. Cells containing the virus are mixed with cryoprotectants to allow storage in liquid nitrogen.

As the vaccine is produced in the United States, it is fully re-tested after importation in Europe. Validation of the potency assay was described in detail and adequately performed.

Batch release data showed consistency and compliance of the product's quality attributes with the specifications.

Data on stability of the active substance in the vaccine have been considered to set release specifications in order to ensure that safe and efficacious vaccines are released. The data provided are acceptable to support the proposed stability in the framework of an authorisation in exceptional circumstances. However, the applicant should report stability result for one batch tested in Europe including results for other tests (sterility, pH, appearance) at the end of the storage period (specific obligation).

In-use stability should be confirmed for this vaccine (specific obligation).

Specific obligations linked to the granting of an authorisation in exceptional circumstances:

-in-use stability data generated with this vaccine should be provided;

-complete stability data for one batch tested in Europe including results for appearance, pH and sterility at the end of the observation period should be provided.

Under the framework of an authorisation in exceptional circumstances, the data provided are considered adequate to support the quality of the product.

Part 3 – Safety documentation (safety and residues tests)

General requirements

Vectormune HVT-AIV is a cell-associated, live recombinant virus vaccine for use in chickens containing live recombinant serotype 3 turkey herpesvirus (HVT) strain FC-126 expressing H5 hemagglutinin from avian influenza virus. No adjuvant is included.

The vaccine is intended to be administered at one day of age by subcutaneous injection (0.2 ml) to stimulate active immunity against AIV. The maximum antigen titre per dose is 12 000 (plaque-forming units) of cell-associated live recombinant rHVT-AI.

Pre-clinical studies have been carried out in SPF eggs or chickens free from antibodies to HVT and AI H5—the most sensitive category.

In the overdose and increase in virulence studies, the master seed virus (MSV) was used. In the spread and dissemination studies, instead of the MSV, a vaccine was used, produced at a passage which is the lowest possible for the finished product has been used. In most studies, groups receiving the non-recombinant parent HVT strain were included for comparison.

Safety documentation

Eight safety studies were conducted to investigate the safety of the product. These included 6 pre-clinical studies investigating the safety of the administration of a 4-fold overdose, spread, increase in virulence safety in target species and reproductive performance, as well as 2 clinical trials. The vaccine was administered by the s.c. route, as recommended, or by the in ovo route (data considered for additional information). Although not GLP-compliant per se, these studies were performed according to USDA quality standards under adequately controlled conditions. This is considered acceptable in accordance with guideline on data requirements for the authorisation of IVMPs under exceptional circumstances.

Pre-clinical studies

Safety of the administration of one dose

No study for the safety of administration of one dose was performed. Instead, overdose safety testing was performed.

Safety of one administration of an overdose

One pivotal study was performed including four groups of 18 days embryonated SPF eggs.

Group 1 was inoculated *in ovo* with 1 dose of vaccine MSV (50000 PFU – more than 4-fold proposed maximum titre). Group 2 was vaccinated by subcutaneous route at 1 day of age after hatching (48000 PFU – 4-fold proposed maximum titre), group 3 was administered HVT strain RB1B at 4 days of age and group 4 was inoculated with solvent only.

Groups 1, 2 and 4 were observed until 120 days of age and group 3 for 50 days. All birds were euthanised and necropsied at the end of the observation period.

Hatchability was not significantly different between the groups. No vaccinated bird showed clinical signs or died during the follow-up period.

The dose administered is less than 10 times the maximum virus titre. Based on the nature of the active substance (HVT is apathogenic and safe in chickens) and the experience with similar vaccine from the applicant registered in Europe (same HVT parent strain / same insertion site), it is expected that the vaccine would be safe after vaccination with 12000 PFU per dose.

On the basis of the results, no safety concerns arose following the administration of an overdose of the vaccine.

Safety of the repeated administration of one dose

No study has been performed as the vaccine is intended to be administered only once to chickens during their lifetime at 1 day of age.

Examination of reproductive performance

No specific study on reproductive performance has been performed. A warning sentence is included in the SPC not to use the products in birds in lay and within 4 weeks before the start of the laying period. Considering nature of the active substance (apathogenic virus for chickens) and vaccine composition no issue is expected and the proposed SPC wording is acceptable.

Examination of immunological functions

No studies were conducted to investigate the effects of the vaccine on immunological functions. The parent HVT virus is non-pathogenic and not known to be immunosuppressive in chickens. The genetic modification did not result in any change of the safety profile of the virus.

Special requirements for live vaccines

Spread of the vaccine strain

The spread of the vaccine strain from vaccinated to unvaccinated chickens was investigated in one study in which 2 groups of 25 SPF, 18 days embryonated eggs were inoculated either vaccine (50000 PFU) or reference HVT parent strain (50000 PFU). Two groups of 15 SPF chicks were respectively placed in contact with the previous groups. Virus (vaccine strain or parent HVT virus) could be re-isolated from white blood cells of vaccinated birds during at least 21 days. However, no spread to in contact chickens could be evidenced.

No dedicated study was conducted to evaluate the excretion of the vaccine strain. However, there is experience with similar vaccines authorised (CEVAC MD HVT, VECTORMUNE ND, ULTIFEND ND IBD) in which the presence of the strain in different type of samples (cloacal swabs, feather tips, environmental samples) was detected by PCR. Considering that the same insertion site in HVT virus was targeted for all these vaccines, it is not expected that rHVT/AI-H5 strain will show a different shedding profile nor would raise any safety concern compared to these vaccines. These data obtained from similar/comparable IVMPs, already authorised, are acceptable according to Guideline on data requirements for authorisation in exceptional circumstances (EMA/CVMP/IWP/251947/2021).

While it may be accepted not to have any new data or data specific to Vectormune HVT-AIV, information on the expected shedding based on data observed with CEVAC MD HVT is reported in the SPC.

Section 3.5. of the SPC contains the following sentence considered to appropriately mitigate the risk of spreading of the vaccine strain: 'Although no spread was demonstrated between chickens, data from similar vaccines built on the same HVT vector suggest that vaccinated chickens may excrete the vaccine strain up to 46 days following vaccination. During this time, the contact of immunosuppressed and unvaccinated chickens with vaccinated chickens should be avoided. The vaccine strain can spread to turkeys. Safety trials have shown that the excreted vaccine strain is not harmful in turkeys. However, appropriate veterinary and husbandry measures such as cleaning and disinfection procedures should be taken to avoid spread of the vaccine strain to turkeys.'

Dissemination in the vaccinated animal

Dissemination of the vaccine strain after vaccination was compared to the one of the HVT parent strain. Two groups of 20 SPF, 18 days embryonated eggs were inoculated either vaccine (50000 PFU) or HVT parent strain (50000 PFU). Virus was isolated from blood, spleen, bursa and thymus from vaccinated chickens at 10 days and 21 days of age. Tissue tropism of the vaccine strain was demonstrated to be similar to the one of parent strain. Dissemination to internal organs and persistence of the vaccine strain is not unexpected based on the known properties of the parent (HVT) strain.

Increase in virulence of attenuated vaccines

The HVT FC-126 strain is naturally apathogenic and it has not been obtained by attenuation. Ph. Eur. monograph 0589 (Marek's disease vaccine, live), states in section 2-3-2: "The test for increase in virulence is required for Marek's disease virus vaccines but not for turkey herpesvirus vaccine strains, which are naturally apathogenic".

Nevertheless, a study was performed to demonstrate the genetic stability and lack of reversion of virulence of rHVT-AI-H5 following 5 consequential passages in chickens. Ten SPF chicks were vaccinated by SC route, at one day of age, with about 4 fold maximum titre of vaccine (MSV). Seven days after vaccination, blood was collected and used to inoculate another group of SPF chickens or CEF cells. Five passages were performed.

Chickens of each passage were monitored daily for adverse reactions and necropsied after 7 days. Virus was recovered after each passage and virus isolated from the 5th passage was used to verify stability of gene through sequencing of key regions for gene insert and gene expression. The results were compared with MSV and HVT parent strain. The results confirm absence of reversion to virulence after 5 passages in day-old chickens and support the genetic stability of the strain.

Biological properties of the vaccine strain

Data are available on safety of high doses of vaccine (2 to 4 doses) in the following non-target species: quails, pheasants, pigeons and turkeys. The non-replicative properties of the vaccine strain were checked on different mammalian cells in vitro.

As the vaccine is a GMO, the nature and properties of the vaccine strain are fully outlined in part III.E of the dossier.

Recombination or genomic reassortment of the strains

As the genome of HVT is not segmented, genomic reassortment cannot occur according to the current scientific knowledge. Event of recombination has been considered by the applicant and is considered very unlikely.

Common vaccination programs involve mixing of HVT viruses from different serotypes which, with data collected so far, did not lead to generation of recombinant strains.

User safety

A user safety risk assessment in accordance with the 'Guideline on user safety for immunological veterinary medicinal products' (EMA/CVMP/IWP/54533/2006) has been provided by the applicant.

The most likely exposure to the product would be via spilling or by accidental self-injection during vaccination of day-old chicks. The type of user of the product would be limited to professional users.

In general, avian herpesviruses are not known to be a hazard to humans. The excipients and the constituents of the vaccine are commonly used on vaccines and do not pose a risk for the user. The same applied to the low levels of gentamicin present in the finished product.

No consequences in case of accidental self-injection are expected from the vaccine constituents.

Adequate user safety recommendations are proposed in the SPC pertaining to the storage of the vaccine ampoules in liquid nitrogen, i.e. the use of personal protective equipment including gloves, spectacles and boots is recommended.

Study of residues

Residue studies are not required.

The excipients listed in the section 2 of the SPC are either allowed substances for which Table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required, or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as they are in this product.

The concentrations of phenol red and gentamicin sulphate are such that they will have no pharmacological activity at the dose administered and will not constitute a risk to the consumer.

A withdrawal period of 'zero days' is deemed appropriate for this vaccine.

Interactions

The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and therefore proposes to include an appropriate statement in Section 3.8 of the SPC. This is considered acceptable.

Clinical studies

Two supportive clinical studies are provided. Although not performed in Europe, these studies provide additional data on safety of the vaccination used in large scale in day-old chickens as recommended in the SPC. The first study performed in Egypt includes vaccination at day old via SC route of 20755 commercial chickens and the second one, performed in the United Stated, includes vaccination at day old of 1800 commercial chickens and 1800 controls. Birds were monitored for mortality and clinical reactions. No adverse reactions have been observed.

In addition, the applicant provided an overview of the sales of the vaccine over the 10 last years (more than 2 billion doses) and reported absence of any reports of safety issues.

Environmental risk assessment

The assessment of the potential risk to the environment of the use of the vaccine was carried out according to the CVMP 'Note for guidance: environmental risk assessment for immunological veterinary medicinal products' (EMEA/CVMP/074/95).

The vaccine strain is not able to spread to unvaccinated chickens and HVT is widely distributed throughout the world. HVT is apathogenic and its characteristics were not changed as a result of the genetic modification. The insert is genetically stable, no reversion to virulence has been observed after 5 inoculation passages in chickens. None of the inserted genetic sequences code for toxic or allergenic transcription products. None of the excipients in the vaccine represent any hazard to the target species or the environment. The product is applied parentally by automatic syringes. The quantity of vaccine per animal is very low and applied only once in the lifetime of the chickens.

Based on the data provided, the ERA can stop in Phase I. Vectormune HVT-AIV is not expected to pose a risk for the environment when used according to the SPC.

Environmental risk assessment for products containing or consisting of genetically modified organisms

For this product, containing a GMO, the requirements stated in sections I.1.8 and IIIb.3E of Annex II of Regulation (EU) 2019/6 apply.

Detailed information on the possible risks for humans and for the environment has been provided.

Information on the origin, methods of recombination, genetic stability, biological properties and genomic sequences of the vaccine strain has been provided.

An assessment of the environmental risk based on the detailed information provided for the GMO has been performed.

Based on the properties of the parent HVT strain, which is not capable of replication in humans or other mammals, and the results of safety studies in chickens and other birds, which support that HVT's apathogenic nature was not changed during the genetic modification, it is concluded that there are no animal health or environmental concerns.

Under the conditions of the recommended use, the environmental risk of the use Vectormune HVT-AIV as well as the risk to public health could be considered as being negligible.

Overall conclusions on the safety documentation

Safety of Vectormune HVT-AIV administered to 1-day old chickens by subcutaneous route was established.

Safety of a 4-fold overdose of the vaccine in target species was investigated. Based on the results obtained it can be concluded that the vaccine is safe for chickens when used in accordance with the recommended schedule and via the recommended route. No macroscopic or microscopic lesions were observed attributable to the vaccine. No visible or palpable local reactions were observed after SC administration of Vectormune HVT-AIV.

Taking into account the knowledge on similar vaccines based on the same vector and construct (insertion of another gene in the same region of the HVT genome), the specific properties of the virus used as vector (HVT virus apathogenis for chickens) and the evaluation of this vaccine under exceptional circumstances, it can be agreed that proposed maximum titre for this vaccine (12000 PFU) has been adequately justified.

Safety is also supported by 2 clinical studies performed outside Europe investigating safety of the vaccine when used at larger scale and by absence of any pharmacovigilance issues after use of more than 2 billion doses of the vaccine for more than 10 years.

Examination of the reproductive performance was not performed and the SPC contains a warning not to use the vaccine in birds in lay and within 4 weeks before the start of the laying period.

Based on the biological properties of the parent HVT virus, there is no indication that the vaccine virus would have negative effect on the immunological functions.

Studies were conducted to establish the potential for spread and dissemination of the vaccine strain. No evidence of spread to unvaccinated chickens was observed; however, shedding of the vaccine can’t be excluded based on PCR positive feather tip samples and knowledge on the parent strain and vaccine active substances based on similar construct. Vaccine was found to be safe for quails, turkeys, pigeons and pheasants. An appropriate warning on possible shedding of the vaccine strain is included in the SPC.

Although not required by the regulation as the vaccine strain is by nature apathogenic, reversion to virulence of the strain was investigated. After 5 sequential passaging on chickens (MSV to MSV+5) the vaccine did not cause clinical signs and symptoms associated with Marek disease. The apathogenic nature of the parental HVT remains stable.

The biological properties of the parental strain seem to be unaffected by the insertion of the HA gene of AIV and their regulatory elements. A possible recombination or genomic reassortment seems to be unlikely.

The user safety was adequately addressed. Regarding possible hazards emanating from storage in liquid nitrogen and the recommended handling of the ampoules, relevant warnings and protective measures have been included in the SPC.

No study of residues was performed. Most of the substances included in the composition of the vaccine are listed in Table 1 of the Annex to Commission Regulation (EU) 37/2010 or in the list of substances considered as not falling within the scope of Council Regulation (EC) 470/2009. Phenol red and gentamicin have no pharmacological activity at the final concentration in the product.

No specific studies on interactions with other immunological or veterinary medicinal products were performed and the standard warnings were included on the product literature, which is acceptable.

The environmental risk assessment shows that the overall risk of the vaccine towards the environment is negligible.

Information concerning the deliberate release of GMOs was provided in the form of appropriate proprietary studies and via scientific literature. The final GMO was shown to be genetically stable over five passages, with no observation of increase of virulence. The insertion of a foreign antigen did not change the non-pathogenicity of the parent virus.

Under the framework of an authorisation under exceptional circumstances, the data provided are considered adequate to support the safety of the product.

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

General requirements

The vaccine is intended for single lifetime application subcutaneously to day-old chickens.

The vaccine is claimed to reduce mortality, clinical signs and virus excretion due to highly pathogenic avian influenza virus of the H5 type with an onset of immunity of 2 weeks and duration of immunity of 19 weeks.

Challenge model

Pre-clinical studies performed by the applicant include challenge with 2 HPAIV strains containing H5 (H5N1/duck/Hungary/11804/2006 – clade 2.2 and H5N2 A/turkey/Minnesota/12582/2015– clade 2.3.4.4.a). Additional data are available in the form of bibliographic citations, which describe studies performed with Vectormune HVT-AIV whose efficacy is assessed using many challenge strains from different clades and origins including sublineages 2.3.4.4.b. isolated in Europe. This clade is considered

the most relevant in the current epidemiological situation.

Efficacy documentation

Overview of key efficacy studies presented in the dossier is presented below:

Study reference	Study title
Applicant's study	Clinical and virological protection against a clade 2.2. HPAI H5 isolates
Palya V et al, 2018	Transmission experiment with a HPAI H5N8 clade 2.3.4.4.b isolate
Steensels et al, 2016	Clinical and virological protection against a clade 2.3.4.4. HPAI H5 isolate
Nassif S et al, 2020	Effect of HVT and AI-H5 MDA on the clinical and virological protection against 3 clade 2.2. H5 isolates OoI
Kylany et al, 2014	1st study on DoI (19 weeks using a clade 2.2.1 HPAI H5 isolate
WBVR, NL	Transmission study - challenge with HPAI H5N1 clade 2.3.4.4.b. isolate
On-going study	2nd study on DoI (up to 100 weeks) using a clade 2.2.1.1. and 2.3.4.4b HPAI H5 isolate

Some additional bibliographic references are also provided in the annex of the dossier. They support efficacy of the vaccine against various challenge viruses H5Nx from different clades. Those are not described in this report since these data are indicative but not fully relevant in the context of this MA application. Only references using challenge with clade 2.3.4.4. or supporting a vaccine claim are described below.

The proposed minimum efficacy dose for Vectormune HVT-AIV was established based on the experience with other vaccines based on the same platform. This is considered acceptable.

Pre-clinical studies

The amount of details available for the studies presented is not fully up to the standard expected in an application for a full marketing authorisation. All available data were considered as a whole to support the efficacy. In view of the current epidemiological situation in Europe, attention was also given to the efficacy demonstrated against recent highly pathogenic virus from H5 type and in particular clade 2.3.4.4.b strains of European origin.

Onset of immunity and influence of maternally derived antibodies

The applicant conducted 1 study to support efficacy of the vaccine in chickens with MDAs. These chickens were derived from parent flocks vaccinated against Marek's disease using an HVT/Rispens vaccine and, half of them, also vaccinated twice with an inactivated AI H5N2 vaccine. From these parent flocks, groups of 20 commercial broiler chickens were vaccinated at day old by the s.c. route with Vectormune HVT-AIV (2000 PFU). Twenty chickens with MDAs against HVT and AIV (10 vaccinates and 10 controls) were challenged 14 days after vaccination with 10^6 HPAIV type H5N1 clade 2.2. (strain A/duck/Hungary/11804/2006) and the remaining ones were challenged in the same way 21 days after vaccination. Twenty chickens with MDAs against HVT only (10 vaccinates and 10 controls) were also challenged at day 14. Protection of 90% to 100% was observed in vaccinated groups against mortality and clinical signs of avian influenza. Eighty percent to 100% mortality was observed in the controls. While significant reduction of virus excretion was observed in the vaccinated birds with MDAs against HVT and AIV after challenge, at 2 and 3 weeks, results were inconclusive for the vaccinated group with MDAs against HVT only. This study supports development of an immune response (onset of immunity)

from 14 days after vaccination in chickens with MDAs against HVT and AIV and shows that presence of MDAs is not expected to interfere with vaccine efficacy against HPAIV from H5 sub-type [H5N1 clade 2.2.]

Duration of immunity

Data from bibliographic sources are provided (see below), but no data on duration of immunity are available from studies performed by the applicant.
The applicant specified that studies were initiated in which efficacy at 4, 20, 40, 55, 72 and 100 weeks post vaccination was established by challenge with 10^6 EID_{50} of HPAIV H5N1 isolate A/Chicken/Egypt/1709-6/2008 (clade 2.2.1.1.), and for 55-weeks test the isolate H5N8 isolate A/chicken/Belgium/807/2017 (clade 2.3.4.4.b) was used. Results from these studies should be provided (specific obligation).

ADDITIONAL INFORMATION FROM BIBLIOGRAPHIC SOURCES

Efficacy against clade 2.3.4.4.b

Two reports allow to support efficacy of the vaccine against HPAIV clade 2.3.4.4.b.

- Publication of V. Palya *et al* (Efficacy of a recombinant turkey herpesvirus AI (H5) vaccine in preventing transmission of heterologous highly pathogenic H5N8 clade 2.3.4.4.b challenge virus in commercial broilers and layer pullets, Journal of Immunological Research, Volume 2018, article ID 3143189) is enclosed in the dossier. Four groups of 20 day-old commercial broilers and 4 groups of 20 day-old commercial layers were included. Two groups of broilers and 2 groups of layers were vaccinated with Vectormune HVT-AIV by s.c. route (0.2 ml – 4746 PFU, estimated based on the storage time of the vaccine before use). Among broilers and layers, 1 vaccinated and 1 control group were challenged with HPAIV of the H5N8 type belonging to clade 2.3.4.4.b (A/goose/Hungary/1030/017/H5N8) 36 days after vaccination (broilers) or 50 days after vaccination (layers). The remaining groups of birds (vaccinated or controls) were placed in contact with the challenged groups (vaccinated or controls).

All chickens were observed for 14 days for clinical signs and mortality. Oro-nasal and cloacal swabs were sampled for 7 days and at day 10 post-challenge for virological examination (quantification of RNA using real time reverse transcriptase (RRT)-PCR).

In broilers: all challenged control broilers died within 2 to 7 days; a high load of HPAI virus was shed, causing mortality in all in-contact control birds within 4 to 12 days post-challenge. In the vaccinated group only 10% of the challenged birds died and no mortality occurred in vaccinated contact birds. Virus shedding was decreased (number of shedder birds and virus load) in vaccinated challenged birds compared to controls and no challenge virus could be re-isolated from in-contact birds. The statistical analysis allows to define the reproduction ratio R in the non-vaccinated broilers as 1.84 (1.11-3.06), whereas R was 0 in the vaccinated broilers.

In layers: challenged control layers died within 7 days. A high load of HPAI virus was shed by these controls, causing mortality in 40% of the in-contact controls. Moreover, 7 out of 20 of the in-contact birds also shed virus at high levels. Among the vaccinated groups no clinical signs nor mortality were observed. Virus shedding was observed in 3 out of 20 vaccinated birds oro-nasally and in 1 bird via the cloaca. The challenge virus was not re-isolated from any in-contact birds. In non-vaccinated layers, the reproduction ratio was 0.69 (0.33-1.44), whereas R was 0 in the vaccinated layers.

Vaccination elicited a good antibody response (4-5 log_2 HI) against homologous antigen. Response against the challenge virus was lower.

This study confirms efficacy of the vaccination when administered to day-old chickens by subcutaneous route in reducing clinical signs, mortality and excretion (number of shedder chickens and decreased quantity of virus shed) and confirms ability of the vaccine to reduce, if not prevent, transmission.

Results of a recent trial performed at the Wageningen Bioveterinary Reseach (WBVR) in the Netherlands are also reported. In this study 10 one-day-old commercial layers were vaccinated with Vectormune HVT-AIV (batch 395-117 - titre less than 5000 PFU) and 10 were kept as controls. Eight weeks later groups of 5 chickens were challenged intrachoanally with 10^6 $DICT_{50}$ HPAIV H5N1 from clade 2.3.4.4.b (isolated in NL in 2021) and the 5 remaining chickens were kept in contact. In control group, 100% of the challenged birds and the contact birds were ill and died (R was determined to be 3.64 (1.89-6.99)) and all chickens in the vaccinated group (challenged and in-contact) were protected. Vaccine was shown to prevent transmission (R was determined to be 0 (0-0.70)).
This additional study provides supporting data on efficacy of the vaccine against current circulating HPAIV from clade 2.3.4.4.b. currently circulating in Europe.

Additional data – Efficacy against clade 2.3.4.4.

Publication of Steensels *et al*, 2016 (Protection afforded by a recombinant turkey herpesvirus-H5 vaccine against the 2014 European highly pathogenic H5N8 avian influenza strain, Avian Diseases 60:202-209, 2016) is enclosed in the dossier. Four groups of 10 SPF birds were included in the study. Two groups were vaccinated at day old with Vectormune HVT-AIV (4000 PFU) by s.c. route and 2 groups were kept as controls. Twenty-eight days after vaccination, the groups were challenged with HPAI virus of the H5N8 type belonging to clade 2.3.4.4. (A/turkey/Germany-MV/R2472/2014) via oculo-nasal route at the dose of 10^5 EID_{50} (2 groups) or 10^6 EID_{50} (the 2 remaining groups). Birds were observed for 14 days for clinical signs and mortality and oro-pharyngeal and cloacal swabs were sampled at 2, 5, 9 and 14 days for virological examination (RRT-PCR). After challenge, 90% to 100% of the controls died within 4 days; the remaining 10% presented clinical signs for 7-12 days before finally recovering. The totality (100%) of the vaccinated birds were protected against mortality and clinical signs. Excretion of the challenge virus was significantly reduced (quantity of virus and/or number of birds excreting) in the vaccinated group compared to the controls regardless of the challenge dose.

An additional publication was also provided: Nassif S *at al*, 2020 (Herpesvirus of turkey vectored avian influenza vaccine offers cross-protection against antigenically drifted H5Nx highly pathogenic avian influenza virus strains, Avian Pathology, DOI: 10.1080/03079457.2020.1790502). In this paper, a study consisting of 7 groups of 20 SPC birds is described. Three of these groups were vaccinated with Vectormune HVT-AIV (6100 PFU) at day old via SC route. Twenty-eight days after vaccination, the chickens were challenged via the intranasal route with 10^6 EID_{50} of one of the following 3 strains of HPAIV: HPAIV H5N1 clade 2.2.1.2. strain A/chicken/Egypt.173CAL/2017; clade 2.3.4.4. strain A/duck/Egypt/BG1099/2018; HPAIV H5N8 clade 2.3.4.4. A/duck/Egypt/FL6/2018. One group was left unchallenged.
Regardless of the challenge strain applied, all birds in the control groups became seriously ill, died or had to be euthanised within 4 days post-challenge. Protection levels of 90%, 90% and 80% against challenge with H5N1, H5N2 and H5N8, respectively, were obtained in the vaccinated chickens. All control animals shed high loads of virus via the respiratory route. In all 3 vaccinated groups 30% to 40% of the birds did not shed virus and shedding was reduced (reduction from 2.8 log_{10} to 3.8 log_{10}) three days after challenge. The extent of shedding rapidly decreased.

Additional data – duration of immunity

A paper from Kilany *et al*, 2014 (Protection conferred by a recombinant turkey herpes avian influenza vaccine in the rearing period in 2 commercial layer chicken breeds in Egypt, Avian pathology, 43:6,514-523) is enclosed in the dossier. In this study, 2 layer chicken breeds (15 chickens per group) were vaccinated at day old by s.c. route and challenged at 19 weeks of age with HPAIV H5N1 strain A/CK/Egypt/128s/2012 (clade 2.2.1.). These groups were compared with a control group of 10 SPF chickens. A significant reduction of mortality in the vaccinated chickens was observed (60-70%) as well as significant reduction of virus excretion.

The study was performed with a challenge strain from clade 2.2.1; from the results it can be concluded that the vaccination confers an immune response for 19 weeks with a challenge strain H5N1 from clade 2.2.1.

Clinical studies

No clinical studies have been conducted with this vaccine. In the frame of marketing authorisation under exceptional circumstances, such studies are not required.

Overall conclusions on the efficacy documentation

Based on the data available it can be concluded that the vaccine is efficacious against highly pathogenic avian influenza viruses of the H5 sub-type in reducing mortality, clinical signs and excretion.

Efficacy of the vaccine against HPAIV containing H5 is based on 2 studies performed for registration of the vaccine in the US, including challenge with HPAIV sub-type H5 from clades 2.2 or 2.3.4.4.a. Despite some deficiencies, these 2 studies could be considered to support efficacy of the vaccine in reducing mortality, clinical signs and virus excretion due to HPAIV of the H5 sub-type. Onset of immunity of 2 weeks after vaccination by s.c. route is demonstrated using a challenge with HPAIV of subtype H5N1, clade 2.2. Duration of immunity was not established by the applicant through a specific study, but supportive publications have been provided, which have been taken into consideration.

Many additional bibliographic data from different sources confirm efficacy of the vaccine against more recent HPAIV sub-type H5 strains currently epidemiologically relevant in Europe. In particular, one bibliographic data and one public report are available, confirming efficacy of the vaccine against challenge with virulent strain from clade 2.3.4.4.b. in reducing clinical signs, virus shedding and reducing, if not preventing, transmission of the virus in vaccinated layers (50 days after vaccination) and broilers (36 days after vaccination). One publication, involving a challenge with a virulent HPAIV strain 2.2.1., supports a duration of immunity of 19 weeks conferred by vaccination.

Minimal titre of 2500 PFU has been justified by the applicant and accepted, based on the available data obtained with this vaccine or with vaccines relying on the same vector.

Under the framework of an authorisation under exceptional circumstances, the data provided are considered sufficient to support the efficacy of the product.

Specific obligations linked to the granting of an authorisation in exceptional circumstances:

Duration of immunity studies: the results from the challenge studies that have been initiated by the applicant should be provided as soon as available.

Part 5 – Benefit-risk assessment

Introduction

Vectormune HVT-AIV is a cell-associated, live recombinant vector vaccine for chickens for subcutaneous injection.

The vaccine contains one active substance: the recombinant live turkey herpes virus (HVT, Marek's disease serotype 3) genetically modified to express the haemagglutinin 5 (H5) encoding the gene of highly pathogenic avian influenza virus (HPAIV) H5N1.

The vaccine is presented as a frozen suspension for injection in flame-sealed ampoules containing 1000, 2000 or 4000 doses. The vaccine is to be reconstituted before use with a sterile diluent to 0.2 ml/dose for subcutaneous use.

Considering the current concerns about the spread of highly pathogenic avian influenza, the application was submitted under Article 25 of Regulation (EU) 2019/6 (exceptional circumstances). Reduced data requirements therefore apply and have been considered in the assessment in line with the guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021).

Benefit assessment

Direct benefit

The benefit of Vectormune HVT-AIV is its efficacy against highly pathogenic avian influenza (HPAI) virus of the H5 sub-type in reducing mortality, clinical signs and virus excretion. Efficacy was established in pre-clinical studies of acceptable quality standards against virulent HPAIV from H5 subtypes, clade 2.2 or 2.3.4.4.a and efficacy of the vaccine against H5N8 clade 2.3.4.4.b is confirmed by scientific paper published in peer reviewed journals or by a public study performed in Netherlands with studies including challenge.

Based on data provided, efficacy is established after challenge 2 weeks after SC vaccination with H5N1 virus clade 2.2., after challenge 35 days in broilers or 50 days in layers with H5N8 virus clade 2.3.4.4.b (bibliographic reference) and H5N1 virus clade 2.3.4.4.b. (public report). Duration of immunity of 19 weeks could be established based on a challenge study performed with HPAIV sub-type H5 from clade 2.2.1. (bibliographic reference).

Additional benefit

Efficacy in reducing virus excretion of HPAIV is expected to contribute to reduction of transmission of the virus as supported in a bibliographic reference involving challenge of vaccinated broilers and layers with a recent strain. Immune response to vaccination is variable. A possible infection in the field would still elicit antibodies to the nucleoprotein in vaccinated birds, making possible to detect an infection using appropriate assay in an appropriate number of chickens and to implement a DIVA strategy. Information on this point is included in the SPC.

Risk assessment

Quality

Information on the development, manufacture and control of the active substance and finished product has been presented. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these, in turn, lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Some specific obligations have been identified: results of a real-time stability study for one batch of vaccine tested in Europe for all final product tests and results of an in-use stability study performed with this vaccine.

Safety

Risks for the target animal

The safety of the rHVT-AI-H5 vaccine strain in chickens vaccinated subcutaneously at the youngest recommended age was confirmed in a safety study of acceptable standard. No adverse effects were observed in any of the vaccinated birds. Pharmacovigilance data resulting from the use of this vaccine for 10 years in many regions of the world have been provided, confirming absence of any safety issues.

Risk for the user

The CVMP concluded that the user safety for this product is acceptable when used according to the SPC recommendations. Safety advice concerning the handling of ampoules stored in liquid nitrogen is included in the SPC.

Risk for the environment

Vectormune HVT-AIV is not expected to pose a risk for the environment when used according to the SPC recommendations. The vaccine strain may spread to unvaccinated birds, in particular turkeys and a relevant warning to mitigate the risk of transmission is described in the SPC.

Risk for the consumer

No concerns have been identified related to consumer safety.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to user and environment and to provide advice on how to prevent or reduce these risks.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status).

The veterinary medicinal product is subject to a veterinary prescription.

Specific obligation to complete the post-marketing authorisation measures for the marketing authorisation in exceptional circumstances are detailed in Annex II of the product information and mentioned below.

Description	Due date
Complete stability data for 1 batch controlled in Europe including results for	November 2026

Description	Due date
appearance and sterility at the end of the observation period	
In-use stability data generated with this vaccine	June 2025
Duration of immunity studies: results of the challenge studies that have been initiated by the applicant should be provided as soon as available.	December 2025

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

"For active immunisation of one-day old chickens or 18-19 old embryonated chicken eggs:
- to reduce mortality, clinical signs and virus excretion due to infection with highly pathogenic avian influenza (HPAI) virus of the H5 type
- to reduce mortality, clinical signs and lesions caused by Marek's disease (MD) virus.
- Onset of immunity: HPAI: 2 weeks of age
  MD: 5 days
- Duration of immunity: HPAI: 19 weeks
  MD: entire risk period

After assessment of the data submitted and taking into account the exceptional circumstances, the CVMP agreed to the following indication(s):
"For active immunisation of one-day old chickens:
- to reduce mortality, clinical signs and virus excretion due to infection with highly pathogenic avian influenza (HPAI) virus of the H5 sub-type
- Onset of immunity: 2 weeks of age
- Duration of immunity: 19 weeks

Information on the development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product has a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk balance is considered positive.

As the application was submitted under Article 25, certain pivotal data relies on studies that do not fully conform to regulatory requirements, such as bibliographic sources including challenges. However, the CVMP considers that the overall benefit of the availability of the veterinary medicinal product could outweigh the risk of absence of these data, also taking into consideration the specific obligations outlined above.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for Vectormune HVT-AIV is approvable since these data satisfy the requirements for an authorisation set out in in the legislation in accordance with Article 25 of Regulation (EU) 2019/6.

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.